REMARKS/ARGUMENT

The withdrawal of claims 8-11 is again noted. It is respectfully that in view of the comments below, there will be an allowable generic or linking claim and these claims should also be examined.

Claims 1-5, 7, 12, 13 and 16-18 have been rejected under 35 U.S.C. § 103 over Schafer in view of Tosa and the newly cited Carter patent. This rejection is respectfully traversed.

The present invention is concerned with a kinetic assay during the course of which a component of the system becomes at least partially bound, directly or indirectly, to the surface of a solid body. The Applicants recognized that during the course of such an assay, a reliable measurement of the bound or absorbed component, i.e., without interference from the free component in the assay system, can be obtained by direct continuous monitoring of the component. This allows an indication of the unknown ligand concentration to be obtained at a very early stage of the incubation period without the need to wait for an arbitrarily determined end point, such as the equilibrium steady state condition. As a result, the operator can observe the result continuously and judge whether it is worthwhile taking further readings in an attempt to improve the accuracy of the results. This continuous monitoring also allows random errors caused by problems with instrumentation, for instance, to be readily identified.

Claim 1 recites the three steps involved in the invention. First, an analyte dependent parameter (such as, for example, a fluorescent emission) is measured kinetically in a direct and continuous manner from a time after the onset of incubation. In the second step, the measured kinetic data is manipulated to quantitatively determine the unknown

sample and in the third step, the results of the determination are monitored continuously. There is no teaching or suggestion of this method in the cited references.

Kinetic measurements have been used in certain prior art immunosensors. Here, the rate of change of signal of the sample containing an unknown quantity of antigen is measured and compared with the same parameter for standards containing a known concentration of the antigen. That technique suffers from the drawback that the assay must be allowed to obtain an arbitrary determined equilibrium at which point a single end point measurement of the signal is made. The speed with which equilibrium is reached may be prohibitively slow, and this, in itself, can introduce errors in the measured rate of change of signal which will be critically dependent on the prevailing conditions. It is not possible in such a system to obtain quick and accurate measurements of the ligand concentration.

The Schäfer reference is an improvement in the known kind of immunoassays. The improvement in Schäfer resides in how to manage those assays, in which the calibration curve $X=f^1(C)$ (where C is the concentration and X is a variable derivable from the measurement of a parameter S which varies during the assay) does not have a monotonous shape (column 6, lines 4-14 and 40-42). Schäfer provides a way to reduce the errors and variables linked to these types of assays which were known at the time of that reference. This is done by using operative discriminative algorithms, as noted in column 4, lines 4-43. The deficiencies in the known kinetic assays are therefore equally applicable to Schäfer.

The Office Action acknowledges that Schäfer differs from the claimed invention in that it performs the immunoreactions in solution rather than a solid surface. That difference is important because in the assay claimed, the component which is directly and

continuously measured becomes bound to a solid body and therefore what is being measured during the assay is only this bound component. That avoids interference with any free component in the solution, thereby providing the advantages described in the present application.

Beyond the foregoing, there is another difference between the invention and Schäfer which requires consideration. Applicants respectfully submit that there is no disclosure in Schäfer of the feature that there is continuous monitoring of the results of the determination while such a feature is an essential feature in the claims of the present invention.

It is respectfully submitted that the Examiner will recognize upon a close reading of Schäfer (and particularly the parts which refer to the analysis runs, which are the parts of the assay in which unknown concentrations of analyte are detected in the test samples) that the results of the determination of a particular test assay are measured only once (at an end point or elsewhere) and are not monitored continuously. In the Abstract, for example, there is a discussion of the steps that take place in an analysis run. It is indicated that an analysis score is calculated from the kinetic measurements ($S(t)$) of the analysis run according to the operative discrimination algorithm which has been calculated from the various training runs carried out with known concentrations of analyte. The score produced is then compared with the boundary score (again worked out from the training runs) and the measurement result is assigned to one of the sub-curves of the calibration curve by comparison of the analysis score with the boundary score. The concentration of analyte in the test sample is then determined using the measurement result to read the concentration from the appropriate part of the standard curve, such as that shown in Figure 2. This determination of concentration is carried out only once in a particular assay with a

particular sample after the analysis score has been determined and analyzed. There is no disclosure or suggestion that the concentration be monitored continuously throughout the assay.

Claim 1 in Schäfer is similar. In step (c), the analysis run which is carried out on a sample of unknown concentration of analyte and the kinetic data measured for the unknown sample, after which a single analysis score is calculated from the kinetic data according to the operative discrimination procedure (i.e., using the operative discrimination algorithm determined from the training runs). In step (d), the single analysis score is compared to the boundary score in order to determine to which part of the calibration curve the input variable should be assigned. The concentration is then determined in step (e) from the input variable "X", reading the appropriate part of the calibration curve. This last step contains no indication or suggestion that the concentration is determined more than once for any particular analysis run with any particular sample and, indeed, there is no suggestion there would be any advantage to carrying out a continuous determination of concentration. The equivalent part of the supporting specification, i.e., column 4, lines 32-43, which describes the invention in its most broadly contemplated form, corresponds to claim 1 and thus also does not describe or suggestion continuous monitoring.

The experimental examples in the reference also do not provide any evidence that the concentration is determined more than once and that the results of the concentration are monitored continuously throughout the assay. This is further apparent when the Figures of the patent showing the results are considered. Figure 1 shows the kinetic measurement with time of an analyte dependent parameter (absorbance) for various concentrations of analyte. That Figure is equivalent to Figure 1 in the present application. However, Figure 2 in the present application goes on to demonstrate that the measured

dose, i.e., the concentration, is also monitored continuously over time (showing the essential feature that the results of the determination are continuously monitored). There is nothing equivalent in Schäfer and indeed, Figure 2 of Schäfer shows the calibration curve, $X = f^1(C)$, from which the concentration of an unknown analyte will be determined by a single input variable "X", combined with the indication from the assay technique as to which part of the curve the input variable "X" has been assigned.

The Office Action refers to column 9, line 63 to column 10, line 11 of Schäfer as indicating continuous calculations for the sample. It is respectfully submitted that this passage does not do so, particularly when read in context of the full disclosure of the reference. The disclosure indicates that the kinetic data measurement takes place at discreet measuring times corresponding to those used in the training run. Once again, the operative discrimination algorithm is applied to the kinetics in order to calculate an analysis score which is then compared to the boundary score allowing assignment of the input variable "X" to one of the subsections of the calibration curve, which allows the concentration to be calculated. The passage thus only refers to a comparison of single analysis score with a boundary score and there is no indication that the determination of concentration occurs more than once in a particular assay.

With respect to the performance of the immunoreactions on a solid surface, the Office Action relies on the Tosa reference as disclosing an assay involving an immunochemical binding reaction on a waveguide surface in order to enable the monitoring of a reaction by luminescence detection. Applicants have previously discussed Tosa in detail in, e.g., the April 2000 Amendment, and incorporate that discussion herein by reference.

The Office Action alleges that it would be obvious to substitute the heterogeneous method of Tosa for the homogeneous method of Schäfer on the grounds that it is an art recognized equivalent method for detecting a binding reaction as well as providing the capability of fast detection response and simplified detector design. In response, Applicants respectfully submit that this is a hindsight justification of the proposed combination and there is no motivation or justification for the combination in the absence of hindsight. Tosa provides no suggestion of a continuous monitoring of results of the determination nor of any possible advantage in carrying out any kinetic measurement. The two references refer to two different kinds of assays and are designed to solve different problems. Schäfer's assay is intended to provide an improved method of assay to overcome the problems of ambiguity associated with homogenous methods of analysis in which the calibration curve does not have a monotonous shape (column 1, line 51 to column 2, line 15 and column 3, lines 60-65). The solution is provided by using a discrimination algorithm (column 3, line 66 to column 4, line 43). Tosa, in contrast, is concerned with providing a new optical waveguide (i.e. heterogeneous) based method for measuring the degree of immunity reaction, which does not involve or suggest a continuous monitoring of results of the determination.

Applicants respectfully submit that the persons skilled in the art would not be motivated to modify the already improved method of Schäfer in any further way. Even in the unlikely event that there was such motivation, then the artisan would not combine the teachings of Schäfer with Tosa as the latter reference relates to a different type of assay and is directed to solving a different type of problem.

In order to overcome the deficiencies in the combination of Schäfer with Tosa, the Office Action cites Carter as an example of providing a waveguide surface for specific

binding assays providing evidence that the heterogeneous technique was well known for providing a number of advantages. In response, Applicant's respectfully submit this additional reference adds nothing further to Tosa which would make the present invention obvious. Applicants have not disputed the fact that heterogeneous assays were known at the time of the present invention. What they are contesting, however, is the implication that it is obvious to combine the two documents or substitute one feature from one document with another to arrive at a very simple solution. In this regard, it is respectfully submitted that if the use of heterogeneous assays such as those described in Carter (1986) was such an obvious substitution, then Schäfer (filed in 1993) would have either made the substitution which is now asserted to be obvious and/or would have suggested that the assays described were also applicable to heterogeneous assays. There is, however, no such disclosure or suggestion in Schäfer. The described methods are concerned solely with assays carried out in solution. Asserting that a heterogeneous assay has certain advantages does not mean it can be substituted for a homogeneous assay. In this connection, Schäfer discusses heterogeneous assays and acknowledges that, similar to homogeneous assays, there are problems associated arising from the fact that the evaluation curve C = f(X) is not unambiguous. See, column 1, lines 34-42. Yet there is no mention in the Schäfer of applying the disclosed improved assay techniques (which solve this problem in a homogeneous assay using an algorithm to assign measurements to the appropriate portion of the evaluation curve) to both homogeneous and heterogeneous assays. If a person skilled in the art would automatically apply any method for homogeneous assays to heterogeneous assays because this would have been advantageous, then surely Schäfer (or some other reference) would have suggested the use of the improved assay techniques with heterogeneous assays, i.e., would have suggested that a heterogeneous method can be

substituted for a described homogeneous method. That disclosure and suggestion is missing.

The Carter reference merely provides an example of an assay in which a layer of an analyte-reactant product is formed at the surface of a waveguide and this causes some modifications in the light signal emitted by reflection from such a surface. It is respectfully submitted that the teachings of this reference go no further than Tosa in establishing that the claimed invention is obvious. The present invention is not taught or suggested in any of the cited references.

Beyond the foregoing, it is respectfully pointed out that Schäfer solves the problems posed by the prior art assays in a completely different matter, i.e. by using operatively discrimination of algorithms, which are determined during the calibration step and that are reported to reduce errors in the measurement results. No such algorithm is necessary according to the present invention because the component becomes bound to the solid surface and can, surprisingly, be measured directly and continuously without interference from the free component in solution. That already reduces errors and variables in the assay. The present invention represents an alternative, more simple solution to the problem solved by Schäfer, and is not taught or suggested in either Schäfer or Tosa/Carter, whether considered alone or in combination.

In light of all of these considerations, it is respectfully submitted that the obviousness rejection should be withdrawn.

Claims 6 and 14 were rejected under 35 U.S.C. § 103 over Schäfer in view of Tosa in further view of Sutherland. As stated in the Office Action, there is no reliance on Carter and given the fact that there is no rejection of claim 1 over Schäfer in view of Tosa, the stated rejection is clearly untenable. Even if Carter is included, given the fact that the

claims on which these rejected claims are dependent are patentable over the combination of Schäfer and Tosa and Carter, it is respectfully submitted that these claims are also patentable. Sutherland does not cure any of the deficiencies in that prior rejection. Sutherland relates to the use of an optical waveguide for optically ascertained parameters of the species and a liquid analyte. It, like Tosa, always uses steady state measurements to establish a relationship between those values. It is therefore respectfully submitted that this rejection should also be withdrawn.

In light of all of the foregoing considerations, it is respectfully submitted that this application is now in condition to be allowed and the early issuance of a Notice of Allowance is respectfully requested.

Respectfully submitted,

Edward A. Meilman

Edward A. Meilman
Registration No.: 24,735
DICKSTEIN SHAPIRO MORIN & OSHINSKY, LLP
1177 Avenue of the Americas – 41st Floor
New York, New York 10036
Telephone: (212) 896-5471